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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,593	11/14/2003	Hua Xu	056274-3451	3233

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FOLEY & LARDNER LLP
1530 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,593	XU ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *October 7, 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *17 and 24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Dose calculator*.

DETAILED ACTION

Election/Restrictions

The Election filed on October 7, 2005 in response to the Restriction Requirement of 04/19/2005 has been entered. Applicant's election of Group I, claims 1-23, as specifically drawn to a method of combination therapy in a mammal comprising administering a therapeutically effective amount of a GST-activated anticancer compound and a therapeutically effective amount of another anticancer therapy has been acknowledged.

Applicant's election with traverse of Group I, claims 1-23 is acknowledged. The traversal is on the ground(s) that the Examiner has required restriction between Claims 1-23 (Group I), drawn to a method, and claims 24-30 (Group II), drawn to materials used in the method. For example, Applicants assert that the Office action alleges as a ground for distinctness that "the process of combination therapy can be practiced with another materially different product such as administering X-ray radiation and orally dosed 9-nitrocamptothecin to a patient (US. 6,281,223, 2001)." However, Applicants argue that the test for distinctness in MPEP 806.05 (h) is whether "the process for using the product as *claimed* can be practiced with another materially different product"(emphasis added). In the instant case, Applicants assert that the process for using the product as claimed is not just "combination therapy" but is (in claim 1) "administering a therapeutically effective amount of a GST-activated anticancer agent and a therapeutically effective amount of another anticancer therapy". Therefore, Applicants contend that because this process can not be practiced with a materially different product (it requires a product containing a GST-activated anticancer agent, and therefore it can not be practiced with radiation and 9-nitrocamptothecin as suggested by the Office action), the claims of Group I and Group II are not distinct under the test of MPEP 806.05 (h).

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants argument that the test for distinctness in MPEP 806.05 (h) is whether "the process for using the product as *claimed* can be practiced with another materially different product"(emphasis added), the Examiner recognizes that a product and a process of using the product can be shown to be distinct inventions if either or both of the following can be shown:

(A) the process of using as claimed can be practiced with another materially different product; or (B) the product as claimed can be used in a materially different process. In the instant case, while Applicants argue that the process cannot be practiced with a materially different product, the presently claimed product, e.g., a pharmaceutical composition comprising a GST-Activated anticancer agent and a chemotherapeutic agent, can be used in a materially different process. For example, the product as claimed can be used in an *in vitro* method of inhibiting cell growth, wherein the *in vitro* method differs from the presently claimed *"in vivo"* method at least in sample population, i.e., cell vs. mammalian subject and route of administration.

Therefore, the restriction is deemed proper and made FINAL.

Claims 1-30 are currently pending

Claims 24-30 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-23 are currently under consideration.

Species Election

Applicant's election of the following species is acknowledged:

- Claims 3-5 wherein S^x is $-S(=O)_2-$.
- Claims 10 and 14 wherein the anticancer therapy is chemotherapy.

Claim 17 has been withdrawn as being drawn to a non-elected species.

Information Disclosure Statement

The Information Disclosure Statements filed on 10/12/2004 and 10/07/2005 have been acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the information disclosure statements. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 18 recites the broad recitation dose of about 60-1280 mg/m^2, and the claim also recites dose of 500-1000 mg/m^2, which is the narrower statement of the range/limitation. Moreover, claim 19 recites the broad recitation dose of about 1-5 weeks, and the claim also recites dose of 1, 2, 3, or 4 week intervals, which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 10-13, 14-15, 18, and 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Jones et al. (US 5,767,147, 1998).

Jones et al. teach a method of combination cancer therapy in a mammal comprising administering a therapeutically effective amount of a haloenol lactone derivative and a therapeutically effective amount of a chemotherapeutic agent (column 10, lines 7-13). With regards

to the haloenol lactone, the patent teaches (column 5, lines 45-67) that the haloenol lactone derivative contains a glutathione thioether, a glutathione-S-Oxide or a glutathione-S-S-dioxide thiol ether. With regards to the chemotherapeutic agent, Jones et al. disclose (column 5, lines 6-11) that the chemotherapeutics include, but are not limited to alkylating agents such as chlorambucil and cyclophosphamide and other chemotherapeutic agents such as adriamycin, vinblastine, actinomycin D and colchicine. With regards to the mammal, the patent teaches (column 9, lines 24-26) that the mammal is a human. Jones et al. further provide (column 10, lines 18-21) that the dose of the haloenol lactone derivative will range from 0.1 to 100 mg/kg body weight. Moreover, the patent teaches (column 10, lines 7-11) a method of potentiating the effect of a chemotherapeutic agent in a mammal, comprising administering a therapeutically effective amount of a haloenol lactone derivative to the mammal being treated with the chemotherapeutic agent. Thus, while Jones *et al.* do not characterize the haloenol lactone derivative as being a "GST-activated anticancer compound", the claimed functional limitation would be an inherent property of the referenced method since the specification discusses (page 8, paragraph 0034) that a "GST-activated anticancer compound" is a compound comprising a glutathione. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). Moreover, while Jones et al do not specifically recite the "dose" in mg/m^2, the claimed limitation appears to be the same as the prior art. For example, administration of 5mg of a haloenol lactone derivative to a male that weighs 81.3 kg would result in a dose of 204.73 mg/m^2, which is well within the ranges recited in the claims (see attached from http://www.fda.gov/cder/cancer/animalframe.htm). Moreover, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the dose of the prior art is different from the claimed dose. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed dose is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 5,767,147, 1998).

Jones et al. teach, as applied above to claims 1-2, 10-13, 14-15, 18, and 21-22, method of combination cancer therapy in a mammal comprising administering a pharmaceutical composition comprising a therapeutically effective amount of a haloenol lactone derivative and a therapeutically effective amount of a chemotherapeutic agent (column 10, lines 7-13). With regards to the haloenol lactone, the patent teaches (column 5, lines 45-67) that the haloenol lactone derivative contains a glutathione thioether, a glutathione-S-Oxide or a glutathione-S-S-dioxide thiol ether. With regards to the chemotherapeutic agent, Jones et al. disclose (column 5, lines 6-11) that the chemotherapeutics include, but are not limited to alkylating agents such as chlorambucil and cyclophosphamide and other chemotherapeutic agents such as adriamycin, vinblastine, actinomycin D and colchicine. With regards to the mammal, the patent teaches (column 9, lines 24-26) that the mammal is a human. Jones et al. further provide (column 10, lines 18-21) that the dose of the haloenol lactone derivative will range from 0.1 to 100 mg/kg body weight. Moreover, the patent teaches (column 10, lines 7-11) a method of potentiating the effect of a chemotherapeutic agent in a mammal, comprising administering a therapeutically effective amount of a haloenol lactone derivative to the mammal being treated with the chemotherapeutic agent.

Jones *et al.* does not explicitly teach that dosing is about 500-100mg/m2 at 1-5 week intervals, especially at 1, 2, 3, or 4-week intervals.

It would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the dosage and interval schedule of the haloenol lactone derivative. One would have been motivated to do so because as taught by Jones et al, the dosages, formulations and administration schedules will vary in cancer patients compared to normal patients (column 10,

lines 17-18). Therefore, where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. As such, one would have a reasonable expectation of success that by optimizing the administration schedule, one would achieve a successful method of treating cancer.

Claims 3-9, 20 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 5,767,147, 1998) in combination with Kauvar et al. (US 5,556,942, 1996, IDS) in further view of USP Dictionary of USAN and International Drug Names (2005, see attached).

Jones et al. teach, as applied above to claims 1-2, 10-13, 14-15, 18-19 and 21-22, a method of combination cancer therapy in a mammal comprising administering a therapeutically effective amount of a haloenol lactone derivative and a therapeutically effective amount of a chemotherapeutic agent (column 10, lines 7-13). With regards to the haloenol lactone, the patent teaches (column 5, lines 45-67) that the haloenol lactone derivative contains a glutathione thioether, a glutathione-S-Oxide or a glutathione-S-S-dioxide thiol ether. With regards to the chemotherapeutic agent, Jones et al. disclose (column 5, lines 6-11) that the chemotherapeutics include, but are not limited to alkylating agents such as chlorambucil and cyclophosphamide and other chemotherapeutic agents such as adriamycin, vinblastine, actinomycin D and colchicine. With regards to the mammal, the patent teaches (column 9, lines 24-26) that the mammal is a human. In particular, Jones et al. teach (abstract) that the haloenol lactone derivatives are useful for treatment of drug resistance in cancer.

Jones et al. does not explicitly teach that the GST-activated anticancer compound is canfosfamide hydrochloride. Nor does Jones et al. teach that the dosing of said canfosfamide hydrochloride is about 500-1000 mg/m2 at 1, 2, 3, or 4 week intervals.

Kauvar et al. teaches (column 5, lines 36-41) a method of treating tumor cells comprising administering glutathione S-transferase-activated compounds (GST), wherein the glutathione-S transferase activated compound are selectively cleaved by the tumor cells to release a cytotoxic agent. With regards the GST-activated anticancer compounds, the patent provides (column 4, lines 22-26 and beginning with column 5, line 1 to column 8, line 53) compounds which appear to be 100% identical to the presently claimed GST-activated anticancer compounds, wherein the GST-

activated compounds comprise a glutathione (GSH) coupled to a leaving group such as a phosphoramide mustard, phosphorodiamidate mustard, a chemotherapeutic agent, toxin, anti-inflammatory or steroid based drugs. In one embodiement, Kauvar et al. disclose a method of treating a tumor comprising administering 300 mg/kg of a GST activated anticancer compound referred to as TER 286 (column 20, lines 21-33). Moreover, the patent teaches (column 4, lines 37-40) that the GST-activated compounds of the invention are useful for the treatment of drug resistance in cancer cells. Furthermore, Kauvar et al. disclose (column 5, lines 42-49) that the GST-activated compounds provide a chemotherapeutic agent to a tumor cell while protecting the function of bone marrow. Although Kauvar et al. do not specifically teach that the GST-activated agent referred to as TER286 is the presently claimed canfosfamide, the claimed limitation would be an inherent property of the referenced compound because as evidenced by USP Dictionary of USAN and International Drug Names, canfosfamide hydrochloride is also referred to as TER 286 (page 155 to 156, last compound taught on page 155). Thus, the claimed compound appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the GST-activated compound does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the haloenol lactone compounds as taught by Jones et al. for the GST-activated compound as taught by Kauvar et al because each of the agents have been individually taught in the prior art to be useful at treating cancer and/or drug resistant tumor cells. Moreover, one would have been motivated to do so because as taught by Kauvar et al., in addition to the compounds being effective at treating cancer and/or drug resistance tumor cells, the GST activated compounds further provide a chemotherapeutic agent to a tumor cell while protecting the function of bone marrow. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting the haloenol lactone compound for the GST-activated compound,

one would achieve a method and/or pharmaceutical composition which protect the function of bone marrow.

Furthermore, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the dosage and interval schedule of canfosfamide hydrochloride. One would have been motivated to do so because as taught by Jones et al, the dosages, formulations and administration schedules will vary in cancer patients compared to normal patients (column 10, lines 17-18). Therefore, where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955), see MPEP § 2144.05 part II A. As such, one would have a reasonable expectation of success that by optimizing the administration schedule, one would achieve a successful method of treating cancer.

Therefore, NO claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Lyttle et al. (US Patent 5,880,097) discloses tethered prodrugs, wherein a biological molecule is coupled to a glutathione derivative.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
11/24/05

Please attach + send to applicants

U. S. Food and Drug Administration • Center for Drug Evaluation and Research

Food and Drug Administration
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Oncology Tools

Dose Calculator

1.) Select Dosage Units: mg/kg ◉ mg/m2 ○

2.) Enter Dosage value: 5

3.) If you wish to modify the default values for **Human** weight and/or height, enter the desired changes below:

Enter weight 81.3 in:

kilograms: ◉ pounds: ○

Enter height ____ in:

centimeters: ○ inches: ○

Calculate

4.) If you wish to modify the default weights (in kilograms) for animal species shown to the right and below, enter desired weight below:

Mouse:	0.02	Rabbit:	2.00
Hamster:	0.03	Cat:	2.50
Rat:	0.15	Monkey:	3.00
Guinea Pig:	1.0	Dog:	8.00

Calculate Reset Defaults

Dose Calculator Results

Please note that for regulatory submissions the FDA recommends the following conversion factors: Mouse = 3, Hamster = 4.1, Rat = 6, Guinea Pig = 7.7. (based on Cancer Chemother Repts 50(4):219(1966)) Multiply the conversion factor by the animal dose in mg/kg to obtain the dose in mg/m2 for human dose equivalent. when both height and weight are known, human body surface area is calculated using Boyd's Formula of Body Surface Area (Boyd E. The growth of the surface area of the human body. University of Minnesota Press. 1935) . Calculations with weight alone (no heigth) are less accurate. All values are estimates and values above 2.25 m2 are not considered accurate

Species	Weight, kg	Est.Total Dose, mg	Dose in mg/kg	Dose in mg/m2	Est. BSA,m2
Human	81.30	406.50	5.00	204.73	1.986
Mouse	0.02	0.10	5.00	15.08	0.007
Hamster	0.03	0.15	5.00	17.28	0.009
Rat	0.15	0.75	5.00	29.52	0.025
Guinea Pig	1.00	5.00	5.00	56.18	0.089
Rabbit	2.00	10.00	5.00	63.00	0.159
Cat	2.50	12.50	5.00	63.42	0.197
Monkey	3.00	15.00	5.00	61.11	0.245
Dog	8.00	40.00	5.00	89.29	0.448

Approved Oncology Drugs | Disease Summaries | Regulatory Tools | Oncology Reference Tools
Patient Liaison Program | Additional Resources | Oncology Tools Home | CDER Home